View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by Elsevier - Publisher Connector

Advanced Drug Delivery Reviews 97 (2016) 260–269

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

ECM and ECM-like materials — Biomaterials for applications in regenerative medicine and cancer therapy☆

Svenja Hinderer [a,b], Shannon Lee Layland [a,b], Katja Schenke-Layland [a,b,c,*]

[a] Department of Women's Health, Research Institute for Women's Health, Eberhard Karls University, Silcherstrasse 7/1, 72076 Tübingen, Germany
[b] Department of Cell and Tissue Engineering, Fraunhofer Institute for Interfacial Engineering and Biotechnology (IGB), Nobelstrasse 12, 70569 Stuttgart, Germany
[c] Department of Medicine/Cardiology, Cardiovascular Research Laboratories, David Geffen School of Medicine at UCLA, 675 Charles E. Young Drive South, MRL 3645, Los Angeles, CA, USA

ARTICLE INFO

Article history:
Received 21 September 2015
Received in revised form 25 November 2015
Accepted 26 November 2015
Available online 3 December 2015

Keywords:
ECM
ECM-like
biomaterials
ECM-mimics
Cancer therapy
Electrospun release systems
Proteins

ABSTRACT

Regenerative strategies such as stem cell-based therapies and tissue engineering applications are being developed with the aim to replace, remodel, regenerate or support damaged tissues and organs. In addition to careful cell type selection, the design of appropriate three-dimensional (3D) scaffolds is essential for the generation of bio-inspired replacement tissues. Such scaffolds are usually made of degradable or non-degradable biomaterials and can serve as cell or drug carriers. The development of more effective and efficient drug carrier systems is also highly relevant for novel cancer treatment strategies. In this review, we provide a summary of current approaches that employ ECM and ECM-like materials, or ECM-synthetic polymer hybrids, as biomaterials in the field of regenerative medicine. We further discuss the utilization of such materials for cell and drug delivery, and highlight strategies for their use as vehicles for cancer therapy.

© 2015 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Contents

1. Introduction

The human body has a great ability to remodel and regenerate small defects. Severe injuries or large defects due to disease or congenital abnormalities are considerably more difficult or impossible for the body to heal on its own. Therefore, regenerative strategies, including stem cell-based therapies and tissue engineering applications, are being developed with the aim to replace, remodel, regenerate or support damaged

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Extracellular Matrix (ECM) and ECM-like materials: Therapeutic Tools and Targets in Cancer Treatment".

* Corresponding author at: Department of Women's Health, Research Institute for Women's Health, Eberhard Karls University, Silcherstrasse 7/1, 72076 Tübingen, Germany. Tel.: +49 7071 29 85205.
E-mail address: katja.schenke-layland@med.uni-tuebingen.de (K. Schenke-Layland).

http://dx.doi.org/10.1016/j.addr.2015.11.019
0169-409X/© 2015 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

tissues and organs or to induce healing by activating the body's self-healing capacity. The tissue engineering approach includes the isolation and culture of specific cell types in either static or bioreactor-controlled dynamic conditions, the generation of artificial tissues by seeding these cells onto three-dimensional (3D) scaffolds, and the implantation of the engineered tissue into the patient [1–3].

Proper design of 3D scaffolds is just as important as careful cell type selection when developing new tissues. The scaffolds are typically made of degradable or non-degradable biomaterials and can serve as cell or drug carriers. Different biomaterials can be used in order to generate 3D scaffolds. Synthetic materials such as poly-L-lactide [4], polyurethane [5] or polyethylene glycol [6] have been used to achieve excellent mechanical support and scaffold stability. Natural materials, which can be structurally weaker when compared to synthetic materials [7], have been successfully used as biomaterials to provide biological cues to cells and surrounding tissues. For example, alginate [8] or chitosan [9] belong to this class of biomaterials, but also extracellular matrix (ECM) or ECM components [10–12] have been used as natural biomaterials.

In this review, we will discuss the use of ECM and ECM-like materials, or ECM-synthetic polymer hybrids, as biomaterials in the field of regenerative medicine, including cell and cancer drug delivery, and their use as vehicles for cancer therapy.

2. ECM and ECM-like materials as implants

The ECM is the natural 3D microenvironment in which cells reside. It is composed of fiber-forming proteins such as collagens and elastic fibers, as well as non-fiber-forming proteins like proteoglycans, glycosaminoglycans and soluble factors [13–15]. The ECM is highly heterogenic and its composition varies from tissue to tissue. Organ-specific cells secrete, assemble and constantly remodel the ECM. Cells bind via cell surface receptors to the ECM, whereby cellular responses such as migration, proliferation and differentiation become activated [14]. Accordingly, the ECM, its components, structural organization and biomechanics, are highly interesting for biomaterials design and fabrication, especially when aiming for implant or test system generation.

2.1. Decellularized materials

First reported in 1948, decellularization aims to isolate the ECM from its inhabiting cells [16]. In this very early research, Poel et al. minced muscle tissue in a wooden box at −70 °C until the tissue was completely homogenized. After centrifugation, they found that some of the cells had been removed from the tissue, and thus began the science of decellularization. One of the first reports of developing decellularized tissue for a therapy was in 1991 where Nrejci et al. combined decellularized human skin, human keratinocytes and fibroblasts to create a reconstituted skin that was transplanted into a mouse model. They showed that the acellular dermis supported keratinocyte attachment, stratification, growth, and differentiation in vivo [17]. In 1995, Badylak et al. first used xenogenic decellularized small intestinal submucosa (SIS) ECM as a biomaterial for Achilles tendon repair [18]. The group demonstrated that the SIS-repaired tendons were stronger than controls and that the SIS degraded within the first 8 weeks post surgery, suggesting that the body began to degrade and replace the SIS with its natural connective tissue in a normal ECM turnover process. The late 90s saw the development of decellularized tissues and organs as implants in the fields of dermal, heart valve, vascular and esophageal tissue engineering [19–23].

Decellularization aims to remove cells from their ECM and thereby removing potential antigens that can cause an inflammatory response or immune-mediated implant rejection [23]. Keane et al. nicely summarized possible events that cause inflammation; such as ineffective decellularization, change of ECM fiber structure, residual detergent or remaining endotoxins [24]. Many different approaches have been used to extract cells from the ECM [24–30]. Since cell and matrix density, morphology and thickness vary from organ to organ, the optimal method for decellularization is highly dependent on the type of tissue [24]. Physical treatments such as agitation, sonication, mechanical pressure, or freeze-thawing procedures, in order to disrupt the cell membrane are commonly combined with extensive washing steps and further chemical processing with ionic solutions and various detergents [23]. Enzymatic treatment using trypsin, dispase, esterases or nucleases has also been employed to remove cells from tissues [30]. Most of the mentioned decellularization techniques have only been assessed in vitro; however, methods like hydrostatic pressure application, enzymatic and detergent treatments are the standard protocols used in daily lab activities and have also been investigated in vivo [27,29,31–34]. Currently published studies and clinical trials strongly focus on chemical detergents, particularly regarding heart valve [34,35], tracheal [32,36] and uterine tissue [37]. After the cellular components are removed, a 3D fibrous and porous ECM structure, mainly composed of collagen fibers, can be maintained [24,38]. The main benefit of a decellularized organ or tissue is the presence of 3D fibrous and porous topographies, as well as macrostructures like the vasculature [24,28]. However, ultrastructural analyses have shown that one major disadvantage of this method is that the process of decellularization potentially damages crucial structural tissue elements such as elastic fibers [26]. Moreover, proteoglycans (PGs) and glycosaminoglycans (GAGs), which connect cells to collagen bundles or elastic fibers and induce a variety of cellular responses, are mainly depleted from decellularized tissues [26]. Since GAGs bind and store high amounts of water, they enable matrices formed by these molecules to withstand high compressive forces [14]. Thus, the loss of PGs and GAGs might have an important impact on ECM structure and integrity, which ultimately translates to implant performance and durability. Bioreactor systems have been developed to instruct reseeded cells to recover GAGs lost due to decellularization [39], although, as shown in a recent study, the body may be the ideal bioreactor for the recellularization, vascularization and personalization of decellularized constructs. For example, Delaere et al. used the body as a bioreactor to condition a native decellularized trachea within the forearm of an implant recipient in an attempt to personalize the construct with the patient's own ECM proteins [40].

Perfusion decellularization techniques have been proposed as a method to manufacture whole organ scaffolds for in vitro implant generation [41]. First used in 2003, Hopper et al. decellularized human placenta as a potential vascularized scaffold for large tissue engineered implants. Large tissues require their own vasculature due to increased tissue thickness where diffusion does not provide the proper oxygen and nutrients for cells [42]. One of the most high profile examples of this was the perfused decellularization and reseeding of a whole human heart. Here, the majority of cells were removed from a whole human heart within 4 to 8 days [43]. Afterwards, the decellularized heart scaffolds were reseeded within 21 days using cardiac progenitor cells (CPCs), mesenchymal stem cells (MSCs), HL-1 cardiomyocytes and human umbilical vein endothelial cells (HUVECs). Interestingly, mature calcium dynamics and electrical coupling were detected in the reseeded heart, and a pumping force of approximately 25% of a fetal heart was detectable [43]. In another study, Hill et al. described a method to decellularize lungs using a bioreactor [44]. The lungs were decellularized by perfusing a hypertonic detergent solution for 2 to 3 h at 37 °C. In this study, the authors intensely analyzed and quantified the remaining ECM proteins and could demonstrate that the acellular lung scaffolds were predominantly composed of structural collagens [44]. Other organs such as the liver were also successfully decellularized and implanted into mice [33,45]. In the field of pediatric oncology, decellularized ovaries were utilized to recapitulate a native endocrine function with the aim to induce puberty after chemotherapy [46].

Decellularized tissues and organs have been brought to market and seen a number of clinical successes. The technique of removing cells and maintaining the 3D ECM construct has already been transferred towards clinical trials [35,47]. Alloderm® (by BioHorizons, Birmingham,

AL, USA) was introduced in 1994 for applications in dentistry [48], and has since been used for burn therapy [49], plastic surgery [50] and hernia repair [51]. Furthermore, an early report on implanted decellularized pulmonary heart valve homografts showed promising results in patients regarding durability [35]. Decellularized bone allografts have been very successful on the market and represent a majority of bone grafts as access to autograft material is limited [52]. Particularly impressive was the success of Mase et al. in the clinical application of a decellularized scaffold in a large quadriceps defect caused by an explosive device. In this study, a 19-year-old marine was treated after 3 years of unsuccessful physical therapy with a multi-layered scaffold composed of ECM derived from porcine SIS. Four months post surgery, the patient showed remarkable gains in isokinetic performance, most likely the result of new tissue that had formed at the implant site [53].

Despite the success of decellularized tissues in the clinical setting, the field has been involved in a number of controversies. The first decellularized porcine heart valves introduced in Europe, Synergraft® (Cryolife Inc., Kennesaw, GA, USA), were implanted into 4 pediatric patients in 2001 — two were homograft (donor organ) replacements and two as part of a Ross operation (replacement of the aortic valve with the patient's own pulmonary valve, and implantation of a substitute in the pulmonary position) [54]. Despite normal recovery and valve function post-surgery, 3 of the 4 children died due to valve failure [54]. Two children suddenly died at 6 weeks and 1 year after implantation due to severely degenerated Synergraft® valves. The third child died at day 7 due to a Synergraft® rupture. The fourth valve was explanted 2 days after implantation [54]. Analyses showed severe inflammation in all valves, which led to failure of the day 7-explant, and degeneration of the valve leaflets and walls in the 6 week and 1 year explants. Histological analysis of the Synergraft® valves also showed an incomplete decellularization of the valves and calcified deposits [54]. The tragic results of this study were the first warning of the dangers of using decellularized tissues, particularly when not properly processed. To ensure that this study remains a single case, non-invasive pre-implantation quality control must be implemented. New, non-invasive and potentially marker-free technologies for quality assessment are essential in order to exclude implant contamination with endotoxins and cellular residues. Multiphoton imaging is a well-established method for the non-invasive analysis of tissue structure post-decellularization or cryopreservation [55]. Other technologies such as Raman microspectroscopy have recently been established to monitor the quality of collagen bundles [56], elastin-containing fibers in heart valve leaflets [57], and proteoglycans [58]. Furthermore, the clinical and scientific community must develop a greater appreciation of the importance of ECM integrity in transplants and implants. Our group previously demonstrated the effect of cardiomyopathy on heart valve leaflet ECM integrity [59]. Despite this evidence, the European community still permits the use of heart valves from donors suffering from cardiomyopathy, in comparison to the US, where such transplants are not allowed. It is our opinion that the impact of ECM damage as a result of decellularization must be further investigated in regards to inflammatory and immune response. For scientists working in the field of decellularization, new protocols that result in tissue with a more consistent ECM integrity are of the upmost importance because tissue standardization will enable the optimization of clinical protocols, which will result in better patient outcomes.

The field of decellularized trachea tissue engineering has had a number of high profile clinical successes. Macchiarini et al. successfully transplanted a decellularized human donor trachea, reseeded with the patient's chondrocytes and epithelial cells, into a 30-year old female patient with end-stage bronchomalacia [60]. The patient was not given immunosuppressive treatment and showed no signs of rejection 3 months after transplantation [60]. However, 5-year follow-up studies showed that the decellularized transplant developed cicatricial stenosis after the first year, which required repeated endoluminal stenting [32]. The decellularized trachea itself appeared normal, completely recellularized, well-vascularized, and had normal ciliary function and mucus clearance [32].

In summary, the field of decellularized tissues is a maturing field that has seen both clinical success and failure. Major shortcomings that must be addressed are the standardization of the decellularization process, and implementation of reliable transplants and implant quality assessment strategies. For example, it had been shown that tissues taken from one or multiple donors that were decellularized by the same protocol showed significantly different ECM compositions after processing [54,61]. Despite the current hurdles, improvement of the efficiency and effectiveness of the decellularization process may translate into more clinical applications. However, the question of whether an unstandardized decellularized tissue is "good enough" for clinical practice or if regulatory agencies will soon require more defined transplants or scaffolds for implants remains to be answered. It is our opinion that the ever more stringent Advanced Therapy Medicinal Product (ATMP) regulations will require defined implants that can be produced in an upscalable and standardized method.

2.2. ECM proteins

There are many proteins in various sizes present in the ECM. Each protein has a unique impact on cell behavior; therefore, using these proteins as biomaterials for regenerative medicine applications potentially enables the generation of functional scaffolds. The choice of the protein or the combination of different proteins depends on the target application and the desired effect. There are many options to acquire these molecules. A common way to obtain native proteins is to isolate them from human or animal tissues [62]; however, the predominant method for biopharmaceutical production is the secretion of recombinant proteins utilizing Chinese hamster ovary cells [63]. Furthermore, so-called artificial or ECM-like proteins are of great interest in biomaterial scaffold production. These molecules can be synthetically generated and are comparable to full-length proteins [64]. They can solely contain a defined molecular weight and can have a specific sequence [64,65].

The following sections focus on methods and techniques to convert ECM and ECM-like proteins to highly functional biomaterial scaffolds.

2.2.1. Coating

Surface modifications play an important role in tissue engineering and regenerative medicine applications as they enhance cell adhesion and potentially improve biocompatibility [66]. A simple way to attach ECM components to the surface of a polymeric substrate is via coating, which is a nonspecific physical adsorption on a surface [66]. The delivery of immobilized bioactive molecules is an attractive method to support tissue regeneration. For example, Ma et al. used this technique to generate a drug release system using dextran sirolimus hybrid coatings [67]. The authors demonstrated an excellent drug release profile and an improved biocompatibility of coated cardiovascular stents [67]. ECM proteins have been successfully used to impact cell behavior. For example, the basement membrane protein collagen type IV was previously applied on surfaces as a coating. Here, the authors impressively demonstrated that collagen type IV coatings allow induced pluripotent stem (iPS) cells to differentiate into functional cells of the cardiovascular and hematopoietic lineage [68]. In another study, a hybrid of fibronectin and gelatin was used as a coating to improve bladder smooth muscle cell adhesion and proliferation [66]. The authors prepared electrospun poly(-carbonate-urea) urethane (PCUU) scaffolds and compared fibronectin-gelatin coated PCUU with the uncoated PCUU specimen [66]. Furthermore, a mixture of collagen type I and chondroitin sulfate was attached onto highly porous poly-ε-caprolactone (PCL) scaffolds to permit cell infiltration [69]. As a result, the authors obtained new skull bone formation, to which they referred to as "ECM-inspired bone formation" [69]. Compared to covalent immobilization, the binding strength by physical adsorption is lower and represents therefore a limitation when aiming

to produce functionalized implants. However, this effect can also be seen as positive for drug releasing systems, since physically adsorped ECM molecules or drugs can be easily released to the surrounding tissue after implantation. This phenomenon makes coating a cost-efficient and highly attractive method to enable drug or ECM delivery. Coating procedures that can be applied right before implantation are, in our opinion, more favorable than coatings applied early in the production process. This allows the application of patient-specific dosages, better scalability and reduces the need to store ECM-containing products that may have a short half-life. In addition, it is advantageous that coating techniques can be performed in aqueous solutions. In alcoholic solutions for example, it has to be considered that alterations of protein structure and function occur [70]. Coating techniques are predominantly used in laboratory setups. A few clinical approaches are documented, where, for example, silver coating was used to avoid bacterial adhesion [71].

2.2.2. Electrospinning

Electrospinning is an attractive method to generate fibrous and porous matrices with a high surface area for regenerative medicine applications. Varying matrix properties, such as fiber and pore sizes, enable the control of cellular responses including migration, proliferation and progenitor cell differentiation [72]. The basic experimental set up for electrospinning includes a syringe, which is connected to a syringe pump, a conductive flat or rotating electrode, also known as the collector, and a high voltage power supply [73]. The polymer solution is pumped through the syringe and forms a droplet on the needle tip. By applying high voltage, the droplet adopts a conical shape, and as soon as the electrical field strength exceeds the surface tension, a thin fiber develops (Fig. 1A). Due to equal charges, instabilities occur and the fiber travels in spinning motions to the collector, the solvent evaporates and a solid fibrous network is generated (Fig. 1B) [74,75].

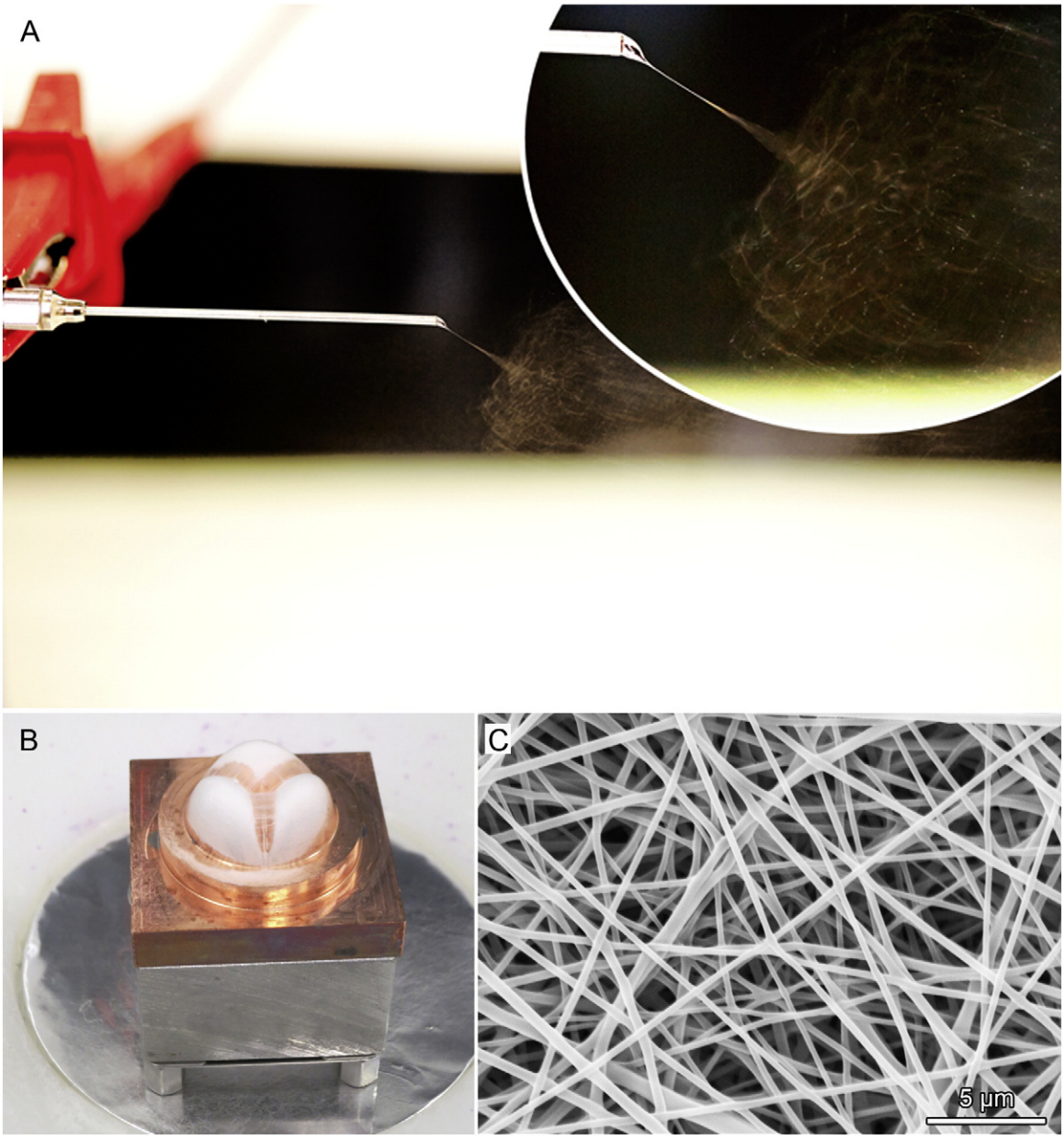

Fig. 1. The electrospinning process. (A) Photograph showing the nozzle, where the polymer solution is pumped through. A droplet forms on the nozzle tip, which adopts a conical shape due to the electrical field. As a result of the electrical field, a fiber forms and travels in spinning motions to the collector. (B) A valve-shaped copper collector with deposited polymer fibers (white) [4]. (C) A scanning electron microscopic image of an electrospun scaffold, showing randomly oriented fibers.

Depending on the collector shape, different scaffold types can be obtained. Therefore, it is possible to spin flat sheets, tubes or even the shape of a heart valve (Fig. 1C). Today, there are various methods described to electrospin synthetic polymers from different solvents [4,75–79]. One of the first examples of electrospinning ECM proteins was performed by the Chaikof group where they spun a 1 wt% solution of type I collagen with polyethylene oxide to create a collagen mesh [80]. Fourteen years after the first ECM scaffolds were spun, groups have electrospun natural decellularized ECM [81] or ECM components such as collagen blends [82], hyaluronan [12] or proteoglycans [76]. Rao et al. used coaxial electrospinning to create an in vitro model of brain white matter to study the migration of malignant brain tumors. In this study, they tested hyaluronic acid, collagen, and Matrigel, an extract of the Engelbreth-Holm-Swarm EHS mouse tumor, in the outer shell of the nanofibers to analyze the effects of different proteins on cell migration [83]. Electrospun scaffolds can be layered using multiple methods. Recently, Huang et al. used positively charged chitosan and negatively charged collagen type 1 to create a layered scaffold to promote wound healing [84]. An overview of electrospun ECM components or hybrids with synthetic polymers and their applications is presented in Table 1. Electrospinning is a simple and cost-effective method to generate 3D fiber-containing materials. However, due to the need of high electrical fields and harsh solvents, it is quite challenging to maintain protein function. Although there are a few publications focusing on functional electrospinning of ECM molecules [76], a clinical translation has not yet been demonstrated.

2.2.3. (Bio)Printing

Printing is a computer-controlled layer-by-layer scaffold fabrication technique. 3D scaffolds can be produced either by laser-based, printer-based or nozzle-based printing, whereas the printer-based method is suitable for printing cells (Fig. 2) [85]. Compared to printing, bioprinting includes the addition of cells, growth factors or other functional elements [86]. It has been demonstrated that ECM proteins are suitable for generating 3D bioprinted scaffolds. Collagens [87], fibrin [88], decellularized ECM [11] and methacrylated gelatin [89] have been employed in bioprinting applications. For example, Hoch et al. introduced living chondrocytes to an in-house manufactured gelatin solution to create a bioink for bioprinting. In their study, the authors showed that the printed chondrocytes exhibited an excellent viability [89], concluding that this method is suitable to generate ECM-based cell carriers for application in cartilage tissue engineering. Due to the layer-by-layer deposition of the material, complex and well-defined 3D structures, such as whole organs can be realized. Recently, Sun et al. developed a printing and coating method termed "Patterning on Topography" (PoT) that enables the layering of proteins such as fibronectin, laminin, collagen type IV, and other ECM proteins onto printed geometric surfaces ranging from smooth to very topographically complex surfaces with high fidelity [90]. In this method that is elegant in its simplicity, thermally sensitive poly(N-isopropylacrylamide) is spin-coated onto glass coverslips and then sandwiched with ECM proteins that have been micro-contact printed with a polydimethylsiloxane stamp. The sandwiched layers are dipped in distilled water and allowed to cool to room temperature [90]. This allows the transfer of the printed ECM protein layer onto the printed topography layer where the ECM adheres via hydrophobic interactions, resulting in a highly defined ECM layered surface that can be used for cell culture or potentially on implant surfaces. In this work, the printed ECM was used to elucidate how competing physical and chemical microenvironment cues influence cardiomyocyte behavior [90]. Soo et al. performed similar work where their group used PoT to investigate the effects of ECM patterns on the migration and differentiation of adult neural stem cells [91]. Using humidified micro-contact printing, Ricoult et al. printed ECM proteins onto smooth surfaces without the need of harsh chemicals that are typically involved in this process, thus protecting the proteins from denaturalization [92]. They created vascularized printed topographies with nanometer

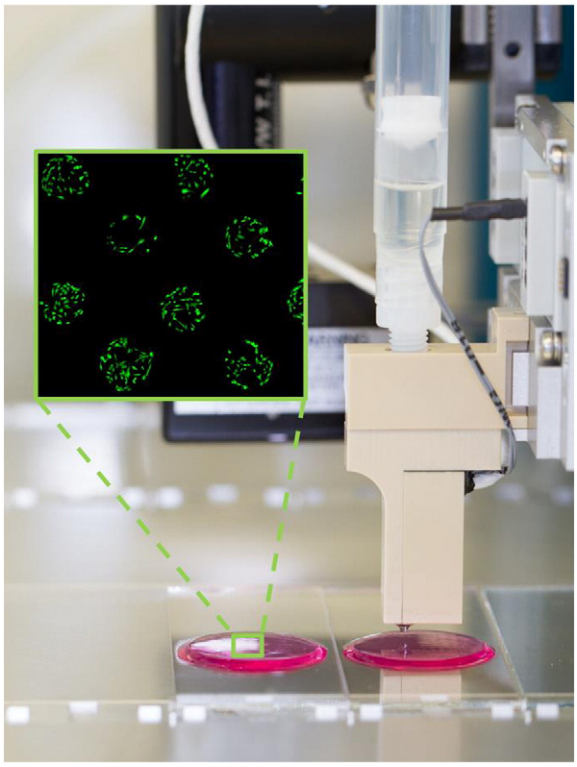

Fig. 2. Bioprinting technique. Bioprinting of methacrylated gelatin with chondrocytes. Patterns of viable chondrocytes are visualized in green.

Table 1
Overview of electrospun ECM components and their biomedical applications.

Polymer	ECM component	Application	Reference
Poly-ε-caprolactone (PCL)	Tropoelastin	Vascular graft	[139]
PCL-gelatin	Decorin	Trachea	[76]
Poly(L-lactide-co-ε-caprolactone)	Collagen type I	Tendon	[140]
Poly(lactic-co-glycolic acid) (PLGA)	Collagen type I	Skeletal muscle	[141]
–	Collagen type I	Artery	[82]
Poly(1,8-octanediol citrate) (POC)	Collagen type I, decorin, aggrecan	Artery	[82]
POC	Collagen type III	Artery	[82]
–	Hyaluronic acid; collagen type I	Cell growth	[142]
PCL	Hyaluronan	Skin	[12]
PLGA	Decellularized ECM	Neural	[81]
PCL	Decellularized ECM	Cartilage	[143]
Polydioxanone	Decellularized ECM	Fat	[144]
Polyethylenoxide	Collagen I; chondroitin-6-sulfate	Tissue regeneration	[145]
–	Laminin(s)	Cell culture	[137]

resolution as a proof of principle for the possibility of the solvent-assisted printing of proteins and nanoparticles [92]. Further options and current applications of 3D bioprinting in regenerative medicine as well as current challenges in the field including improvement of resolution, generation of more adequate printable biomaterials and upscaling to clinical relevant sizes are intensively reviewed by Murphy and Atala [86]. 3D printed scaffolds have already been used in clinical trials treating tracheal [93] or craniofacial [94] defects. Although the advantages of ECM molecules are well known, their introduction to the printing process results in decreased mechanical strengths and thus still remains challenging [86]. To date, a collagen-based material has already been used in a small animal model for wound healing purposes [95]; however, there are no reports on clinically employed bioprinted ECM scaffolds.

2.2.4. Hydrogels and cell sheets

Hydrogels prepared from natural ECM or ECM components can either be loaded with drugs or small molecules, or, since they already contain biochemical information, can be applied alone. Tropoelastin is an ECM protein that induces several cell responses and which is known to be non-thrombogenic [96]. Therefore, tropoelastin is a very promising biomaterial for regenerative medicine purposes. Under physiological conditions, tropoelastin molecules self-organize into spherical nanoparticles that coalesce and form a porous hydrogel when adding crosslinking agents, such as glutaraldehyde [64]. In general, the gelation process is Ca^{2+} [97], pH [98] or phosphate [9] dependent or can be induced by light [99] or enzymes [100]. Collagen type I also forms a solid hydrogel when changing the pH [101]. Xu et al. published an interesting study where they attached a tyramine moiety to hyaluronan [100]. The modified hyaluronan formed a hydrogel when interacting with horseradish peroxidase. In an in vitro study the authors showed that the hydrogel enables the expansion of embryonic stem cells while maintaining their pluripotent state [100].

Single ECM proteins can be used to form stable hydrogels, but also whole ECMs have been used as hydrogel scaffolds. For this purpose, tissues such as omentum [102] or myocardium [103] where decellularized and the acellular matrices were then further processed to form a hydrogel. After several preclinical feasibility studies [103], the myocardial matrix hydrogel is currently considered for clinical trials, since it promotes functional improvement of the post-infarcted heart [103]. Furthermore, in situ polymerizing injectable hydrogels like Novocart® Inject are used routinely to replace cartilage defects [104]. Overall, great progress has been made in demonstrating the potential of hydrogels either as scaffolds for tissue engineering applications or as drug carriers [6].

Another interesting approach to generate ECM-based biomaterials is the cell sheet technique: Under defined in vitro culture conditions, cells are instructed to produce their own ECM, resulting in a scaffold-like biomaterial (Fig. 3) [105]. These cell-produced sheets can be used to deliver cells, drugs as well as proteins to the site of injury in order to initiate regeneration [106]. L'Heureux et al. impressively demonstrated that fibroblast-derived cell sheets have an adequate strength and thickness to serve as a tissue-engineered blood vessel [107]. In this study, a fibroblast-derived cell sheet was produced, rolled up to form a blood vessel, and decellularized in order to obtain an acellular human-based ECM-scaffold. The engineered blood vessel was then reseeded with patient-derived cells [107]. Other cell-produced materials have already found their way into clinical trials and are currently utilized to support damaged cornea [108], heart muscle [109] or cartilage [110], or are used as in vitro-engineered blood vessel substitutes [111]. Interestingly, it was also suggested that by layering multiple cell sheets, organ development could potentially be enabled [112]. Cell sheets nicely resemble the ECM, but a clear limitation is the time that is needed in order to generate these materials. Both, cell sheets as well as ECM-based hydrogels were studied intensely in vitro and have already been successfully applied in clinical trials.

3. ECM and ECM-like materials as vehicles for safe and targeted cell and drug delivery

ECM and ECM-like materials have great potential as cell and drug carriers. A current project supported by the European Union called AMCARE (Advanced Materials for Cardiac Regeneration) is a great example to highlight the relevance and the feasibility of the topic [113]. The main goal of AMCARE is to improve the function of the myocardium after myocardial infarction (MI) by developing an injectable hydrogel for endocardial applications (Cardiogel), and an electrospun patch for epicardial applications (Cardiopatch). Hyaluronic acid is the main component of the hydrogel and patch. These constructs serve as vehicles for targeted delivery of cardiopoietic cells and growth factors in order to improve heart function post MI [113]. Skin wound healing has been already realized with ECM-based drug releasing systems [10,114]. For example, injecting a collagen hydrogel loaded with micro-RNA 29b into full thickness wounds in rats, resulted in an improved remodeling of the skin's ECM [10]. Additionally, a mixture of two ECM proteins – collagen and hyaluronic acid – has been shown to be a suitable drug carrier for skin applications [114]. This ECM-based system demonstrated the impressive effects on the wound healing capacity when loaded with antibiotics and growth factors [114]. To date, growth factors [114,115], antibiotics [114], hydrophobic drugs [116] and inhibitors [117] have been encapsulated and successfully applied using hyaluronic acid-based delivery systems. Hyaluronic acid was used as a γ-secretase inhibitor carrier to treat rheumatoid arthritis [117]. Furthermore, elastin-like peptides (ELPs) were identified as an interesting drug carrier, since drugs can easily be chemically conjugated [118]. Another advantage is that ELPs are synthesized from amino acids and therefore their rate of degradation can be easily programmed [118]. Dreher et al. generated a temperature responsive ELP doxorubicin conjugate, which was delivered to solid tumors as a cancer therapy [119]. In

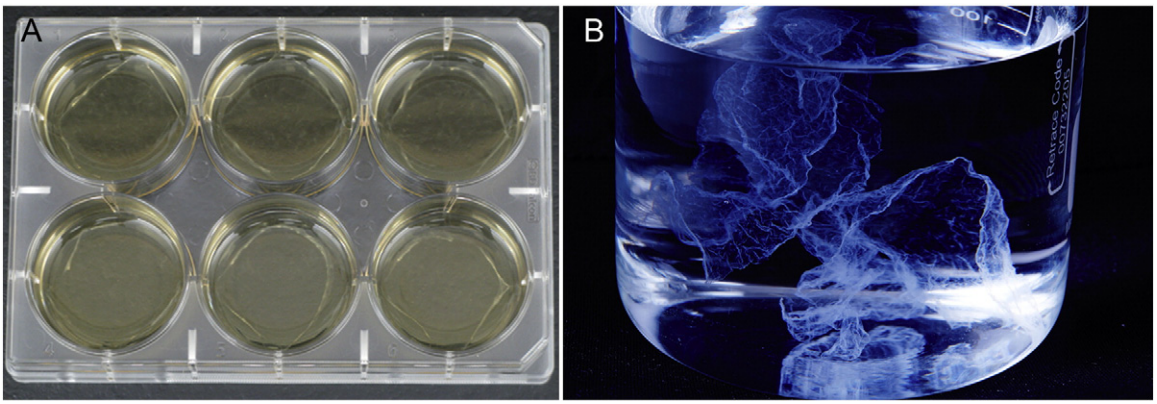

Fig. 3. Fibroblast-derived ECM sheets. (A) Fibroblast-produced, cell and ECM containing sheets in a 6-well plate. (B) ECM sheet after decellularization in PBS.

addition to drug delivery, ECM and ECM-like components can also be used as cell carriers [89,120–122]. A multitude of ECM and ECM-like materials are used in the field of cartilage engineering [89,118,123]. For cartilage applications, chondrocytes have been encapsulated into hydrogels in order to enable an autologous chondrocyte transplantation. Products like the hyaluronic acid-based Novocart® 3D and Inject [104,123] or the fibrin-containing Chondron™ [124] have already been considered in clinics. Another suitable biomaterial is collagen, which has been shown to have a great potential when aiming to deliver mesenchymal stem cells for bone repair [120]. Furthermore, the strength of collagen as a skin substitute with autologous cells has already been described in detail [2,125]. An interesting approach for targeted cell delivery is the use of hyaluronic acid [121,122]. Injectable thermoreversible hyaluronan-based hydrogels have been developed to host nucleus pulposus cells [121]. Hyaluronan-based hydrogels can be produced as shear-thinning hydrogels [122]. Gaffey et al. developed a promising system where endothelial progenitor cells were delivered to the infarcted myocardium using hyaluronan-based shear-thinning system [122]. This methodology enabled direct cell delivery and cell retention in order to enhance vasculogenesis and improve myocardial function [122]. In our opinion, the immobilization of cells and drugs on carriers is important in order to enable a precise and targeted application as well as a controlled release over time. Using ECM molecules to design these carriers results in a potentially mechanically weaker but biologically more relevant and biocompatible system.

4. Electrospun release systems for cancer therapy

Electrospun scaffolds from synthetic polymers, natural proteins or hybrid materials are frequently utilized to generate drug-eluting systems [74]. In the following section, we aimed to highlight the potential for local applications of chemotherapeutics via electrospun scaffolds. A simple way to enable bioactive molecule release is to perform scaffold coating, as discussed in a previous section of this review article. Compared to flat membranes, electrospun scaffolds have the advantage of an enlarged surface area due to the fibrous structure [126,127]. In this case, more proteins, growth factors or drugs can be delivered to the region of interest. Another approach is the direct electrospinning of bioactive substances, which are then present on the fiber surface and within the fiber [76,128]. A release can then be realized using degradable polymers like PCL, polyethylene oxide (PEO) or poly(lactic-co-glycolic) acid (PLGA) [76,129,130]. This technique has already been demonstrated by electrospinning an emulsion of aqueous decorin with PCL [76]. In this study, the proteoglycan decorin was still functional after the electrospinning process [76], and as decorin is known for its anti-angiogenic properties [15], this substrate could potentially be used for tumor suppression purposes. A sustained drug release and tumor growth inhibition was also shown with an electrospun scaffold prepared from a solution containing PLGA and the mitotic inhibitor drug paclitaxel [126]. Using the same degradable polymer for electrospinning, Sampath et al. intensively studied release profiles of curcumin, which is described to be favorable for carcinoma treatment [129]. Moreover, the anticancer drug doxorubicin was successfully electrospun as a multicomponent hybrid including PEO, chitosan and graphite oxide [130].

In addition to coating or direct electrospinning, there is a third method named coaxial electrospinning to encapsulate drugs [75]. For a coaxial set-up, a needle-in-needle construction, as well as two injection pumps are required [131]. The inner needle is then perfused with the bioactive agent, whereas the outer needle contains the solution of a degradable polymer (Fig. 4) [131,132]. The resulting fibers are called core-sheath fibers [131]. As soon as the polymer degrades, the sheath gets porous and the drug elutes to the surrounding space. This set-up has been used to provide drug delivery systems for cancer therapies [131]. Doxorubicin, for example, was encapsulated in a polyvinyl alcohol/chitosan sheath [131]. In another study the same drug was coaxial

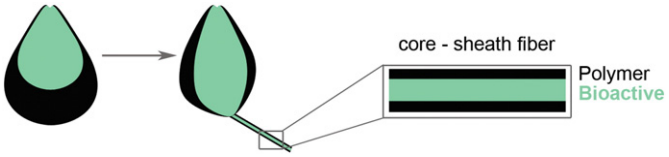

Fig. 4. Principle of coaxial electrospinning. The inner needle contains a solution of the functional molecule (green), whereas the outer needle is filled with a degradable polymer (black). The resulting fiber has a core and a degradable sheath. As soon as the sheath degrades, the functional molecules release to the surrounding extracellular space.

electrospun using crosslinked gelatin as the sheath. Here, the doxorubicin was delivered as micelles. Therefore, doxorubicin-PCL-PEG micelles were assembled first, followed by coaxial electrospinning [133]. To date, there is no electrospun release system that is clinically approved and applied for cancer treatment; however, there are many interesting, successful and promising in vivo and in vitro studies, indicating the enormous potential of electrospun biomaterials as drug delivery systems for cancer therapies.

5. ECM-mimics

The ECM provides chemical, physical and biological cues affecting cellular function as a result of signal transduction via cell surface receptors [14]. A new and promising approach is to produce scaffolds that mimic the mechanical and biophysical properties of the ECM. The ECM is considered as a natural scaffold or biomaterial, which needs to be precisely analyzed and imitated in order to generate functional scaffolds for regenerative medicine or drug delivery applications [134]. The native ECM is a reservoir for biochemical signals, undergoing permanent remodeling processes [135]. It is well known that cells respond to biochemical and biophysical cues; however, the synergistic and antagonistic relationship between them and other events taking place in the ECM is not completely understood [135] and is therefore quite challenging to mimic. The structure and architecture of a native heart valve was mimicked using electrospinning as a fiber forming technique [4]. In this study, the authors also identified mechanical characteristics such as Young's modulus, tensile strength, expansion and water uptake capacity, and designed a scaffold based on these values [4]. In a similar study, a scaffold was generated to mimicki the mechanical properties of adipose tissue [136]. Today, many concepts exist to additionally include biological cues. Neal et al. mimicked the morphological and biological properties of the basement membrane by producing a laminin fiber network [137]. Another way to introduce biological information is specific surface modification, such as ECM-inspired coatings [69,138].

The ECM is a highly complex network that varies in its composition from tissue to tissue and organ to organ. Although it is clearly not easy to resemble all facets of the ECM, different studies demonstrated that it is important to get inspired by the native ECM when aiming for the design of biomaterial-composed scaffolds. By mimicking the natural ECM, it is possible to control physical and mechanical properties, as well as cell growth or drug release, which is an important step towards smart implants with a regenerative potential.

6. Conclusion

ECM and ECM-like materials have a great potential to serve as natural or nature-mimicking scaffolds in the field of regenerative medicine. Many studies have successfully demonstrated that these materials can be used as vehicles to deliver cells and drugs to the human body. Compared to ECM biomaterials, synthetic polymers are more favorable in terms of mechanical loading as well as reproducibility, since their synthesis can be easily controlled. Another benefit of synthetic biomaterials is the ability of producing cost-efficient carriers. However, despite these

considerable advantages, there is a great interest in the utilization of ECM and ECM-like biomaterials as potential cell and drug carriers, promoted by an unmet need of fully functional and biocompatible materials. Synthetic polymers are inert and in most cases do not sufficiently interact with the surrounding cells. In order to address functionality, biocompatibility and material integration to the tissue, a more physiological microenvironment needs to be created by using, for example, ECM molecules. By utilizing these highly functional materials, the induction of tissue or organ remodeling and regeneration is possible. Furthermore, these superior biomaterials have already been investigated for cancer treatment, for which they seem to be promising drug delivery vehicles. Although most of the approaches discussed in this review reflect proof-of-principal or animal studies, research teams all over the world are working to translate these accomplishments into clinical reality in order to provide safer transplants and implants, improve cell and drug delivery strategies, and design more efficient cancer therapies.

Acknowledgments

The authors thank Dr. Eva Hoch (University of Stuttgart) for providing Fig. 3. The authors are grateful for the financial support by the Fraunhofer-Gesellschaft (TALENTA to S.H.; FFE to S.L.L.), as well as the Medical Faculty of the Eberhard Karls University Tübingen, the Fraunhofer IGB Stuttgart, the Ministry of Science, Research and the Arts of Baden-Württemberg (33-729.55-3/214 and SI-BW 01222-91), the Deutsche Forschungsgemeinschaft (SCHE 701/7-1), and the European Union (604531 AMCARE, FP7-NMP-2013-SME-7) (all to K.S.-L.).

References

[1] U.A. Stock, J.P. Vacanti, Tissue engineering: current state and prospects, Annu. Rev. Med. 52 (2001) 443–451.
[2] F. Groeber, M. Holeiter, M. Hampel, S. Hinderer, K. Schenke-Layland, Skin tissue engineering — in vivo and in vitro applications, Adv. Drug Deliv. Rev. 63 (2011) 352–366.
[3] K. Schenke-Layland, F. Opitz, M. Gross, C. Doring, K.J. Halbhuber, F. Schirrmeister, T. Wahlers, U.A. Stock, Complete dynamic repopulation of decellularized heart valves by application of defined physical signals—an in vitro study, Cardiovasc. Res. 60 (2003) 497–509.
[4] S. Hinderer, J. Seifert, M. Votteler, N. Shen, J. Rheinlaender, T.E. Schäffer, K. Schenke-Layland, Engineering of a bio-functionalized hybrid off-the-shelf heart valve, Biomaterials 35 (2014) 2130–2139.
[5] N. Baheiraei, H. Yeganeh, J. Ai, R. Gharibi, M. Azami, F. Faghihi, Synthesis, characterization and antioxidant activity of a novel electroactive and biodegradable polyurethane for cardiac tissue engineering application, Mater. Sci. Eng. C Mater. Biol. Appl. 44 (2014) 24–37.
[6] M.K. Schesny, M. Monaghan, A.H. Bindermann, D. Freund, M. Seifert, J.A. Eble, S. Vogel, M.P. Gawaz, S. Hinderer, K. Schenke-Layland, Preserved bioactivity and tunable release of a SDF1-GPVI bi-specific protein using photo-crosslinked PEGda hydrogels, Biomaterials 35 (2014) 7180–7187.
[7] M.G. Cascone, B. Sim, D. Sandra, Blends of synthetic and natural polymers as drug delivery systems for growth hormone, Biomaterials 16 (1995) 569–574.
[8] J. Yu, Y. Gu, K.T. Du, S. Mihardja, R.E. Sievers, R.J. Lee, The effect of injected RGD modified alginate on angiogenesis and left ventricular function in a chronic rat infarct model, Biomaterials 30 (2009) 751–756.
[9] H. Wang, J. Shi, Y. Wang, Y. Yin, L. Wang, J. Liu, Z. Liu, C. Duan, P. Zhu, C. Wang, Promotion of cardiac differentiation of brown adipose derived stem cells by chitosan hydrogel for repair after myocardial infarction, Biomaterials 35 (2014) 3986–3998.
[10] M. Monaghan, S. Browne, K. Schenke-Layland, A. Pandit, A collagen-based scaffold delivering exogenous microRNA-29B to modulate extracellular matrix remodeling, Mol. Ther. 22 (2014) 786–796.
[11] F. Pati, J. Jang, D.-H. Ha, S. Won Kim, J.-W. Rhie, J.-H. Shim, D.-H. Kim, D.-W. Cho, Printing three-dimensional tissue analogues with decellularized extracellular matrix bioink, Nat. Commun. 5 (2014).
[12] Y. Qian, L. Li, C. Jiang, W. Xu, Y. Lv, L. Zhong, K. Cai, L. Yang, The effect of hyaluronan on the motility of skin dermal fibroblasts in nanofibrous scaffolds, Int. J. Biol. Macromol. (2015), http://dx.doi.org/10.1016/j.ijbiomac.2015.04.059.
[13] R.P. Mecham, Overview of extracellular matrix, Curr. Protoc. Cell Biol. 57 (2001) 10.11.11–10.11.16.
[14] C. Frantz, K.M. Stewart, V.M. Weaver, The extracellular matrix at a glance, J. Cell Sci. 123 (2010) 4195–4200.
[15] L. Schaefer, R.M. Schaefer, Proteoglycans: from structural compounds to signaling molecules, Cell Tissue Res. 339 (2010) 237–246.
[16] P. WE, Preparation of acellular homogenates from muscle samples, Science 108 (1948) 390–391.
[17] N.C. Krejci, C.B. Cuono, R.C. Langdon, J. McGuire, In vitro reconstitution of skin: fibroblasts facilitate keratinocyte growth and differentiation on acellular reticular dermis, J. Investig. Dermatol. 97 (1991) 843–848.
[18] S.F. Badylak, R. Tullius, K. Kokini, K.D. Shelbourne, T. Klootwyk, S.L. Voytik, M.R. Kraine, C. Simmons, The use of xenogeneic small intestinal submucosa as a biomaterial for Achilles tendon repair in a dog model, J. Biomed. Mater. Res. 29 (1995) 977–985.
[19] B.J. Reagan, M.R. Madden, J. Huo, M. Mathwich, L. Staiano-Coico, Analysis of cellular and decellular allogeneic dermal grafts for the treatment of full-thickness wounds in a porcine model, J. Trauma 43 (1997) 458–466.
[20] M.F. O'Brien, S. Goldstein, S. Walsh, K.S. Black, R. Elkins, D. Clarke, The SynerGraft valve: a new acellular (nonglutaraldehyde-fixed) tissue heart valve for autologous recellularization first experimental studies before clinical implantation, Semin. Thorac. Cardiovasc. Surg. 11 (1999) 194–200.
[21] A. Isch, S.A. Engum, C.A. Ruble, M.M. Davis, J.L. Grosfeld, Patch esophagoplasty using AlloDerm as a tissue scaffold, J. Pediatr. Surg. 36 (2001) 266–268.
[22] S. Kaushal, G.E. Amiel, K.J. Guleserian, O.M. Shapira, T. Perry, F.W. Sutherland, E. Rabkin, A.M. Moran, F.J. Schoen, A. Atala, S. Soker, J. Bischoff, J.E. Mayer Jr., Functional small-diameter neovessels created using endothelial progenitor cells expanded ex vivo, Nat. Med. 7 (2001) 1035–1040.
[23] T.W. Gilbert, T.L. Sellaro, S.F. Badylak, Decellularization of tissues and organs, Biomaterials 27 (2006) 3675–3683.
[24] T.J. Keane, I.T. Swinehart, S.F. Badylak, Methods of tissue decellularization used for preparation of biologic scaffolds and in vivo relevance, Methods 84 (2015) 25–34.
[25] J. Arenas-Herrera, I. Ko, A. Atala, J. Yoo, Decellularization for whole organ bioengineering, Biomed. Mater. 8 (2013) 014106.
[26] S. Hinderer, K. Schenke-Layland, Tracheal tissue engineering: building on a strong foundation, Expert Rev. Med. Devices 10 (2013) 33–35.
[27] K. Schenke-Layland, O. Vasilevski, F. Opitz, K. König, I. Riemann, K.J. Halbhuber, T. Wahlers, U.A. Stock, Impact of decellularization of xenogeneic tissue on extracellular matrix integrity for tissue engineering of heart valves, J. Struct. Biol. 143 (2003) 201–208.
[28] B. Andrée, K. Bela, T. Horvath, M. Lux, R. Ramm, L. Venturini, A. Ciubotaru, R. Zweigerdt, A. Haverich, A. Hilfiker, Successful re-endothelialization of a perfusable biological vascularized matrix (BioVaM) for the generation of 3D artificial cardiac tissue, Basic Res. Cardiol. 109 (2014) 1–13.
[29] A. Porzionato, M. Sfriso, A. Pontini, V. Macchi, L. Petrelli, P. Pavan, A. Natali, F. Bassetto, V. Vindigni, R. De Caro, Decellularized human skeletal muscle as biologic scaffold for reconstructive surgery, Int. J. Mol. Sci. 16 (2015) 14808.
[30] S. Badylak, Decellularized allogeneic and xenogeneic tissue as a bioscaffold for regenerative medicine: factors that influence the host response, Ann. Biomed. Eng. 42 (2014) 1517–1527.
[31] E.G. Santoso, K. Yoshida, Y. Hirota, M. Aizawa, O. Yoshino, A. Kishida, Y. Osuga, S. Saito, T. Ushida, K.S. Furukawa, Application of detergents or high hydrostatic pressure as decellularization processes in uterine tissues and their subsequent effects on in vivo uterine regeneration in murine models, PLoS ONE 9 (2014) e103201.
[32] A. Gonfiotti, M.O. Jaus, D. Barale, S. Baiguera, C. Comin, F. Lavorini, G. Fontana, O. Sibila, G. Rombolà, P. Jungebluth, P. Macchiarini, The first tissue-engineered airway transplantation: 5-year follow-up results, Lancet 383 (2014) 238–244.
[33] H. Zhang, Y. Zhang, F. Ma, P. Bie, L. Bai, Orthotopic transplantation of decellularized liver scaffold in mice, Int. J. Clin. Exp. Med. 8 (2015) 598–606.
[34] B. Weber, P.E. Dijkman, J. Scherman, B. Sanders, M.Y. Emmert, J. Grünenfelder, R. Verbeek, M. Bracher, M. Black, T. Franz, J. Kortsmit, P. Modregger, S. Peter, M. Stampanoni, J. Robert, D. Kehl, M. van Doeselaar, M. Schweiger, C.E. Brokopp, T. Wälchli, V. Falk, P. Zilla, A. Driessen-Mol, F.P.T. Baaijens, S.P. Hoerstrup, Off-the-shelf human decellularized tissue-engineered heart valves in a non-human primate model, Biomaterials 34 (2013) 7269–7280.
[35] S. Cebotari, I. Tudorache, A. Ciubotaru, D. Boethig, S. Sarikouch, A. Goerler, A. Lichtenberg, E. Cheptanaru, S. Barnaciuc, A. Cazacu, O. Maliga, O. Repin, L. Maniuc, T. Breymann, A. Haverich, Use of fresh decellularized allografts for pulmonary valve replacement may reduce the reoperation rate in children and young adults: early report, Circulation 124 (2011) S115–S123.
[36] P. Macchiarini, P. Jungebluth, T. Go, M.A. Asnaghi, L.E. Rees, T.A. Cogan, A. Dodson, J. Martorell, S. Bellini, P.P. Parnigotto, S.C. Dickinson, A.P. Hollander, S. Mantero, M.T. Conconi, M.A. Birchall, Clinical transplantation of a tissue-engineered airway, Lancet 372 (2008) 2023–2030.
[37] F. Costa, P. Dohmen, E. Vieira, S.V. Lopes, C. Colatusso, E.W.L. Pereira, C.N. Matsuda, S. Cauduro, Operação de Ross com homoenxertos valvares decelularizados: resultados de médio prazo, Rev. Bras. Cir. Cardiovasc. 22 (2007) 454–462.
[38] L. Utomo, M. Pleumeekers, L. Nimeskern, S. Nürnberger, K. Stok, F. Hildner, G. van Osch, Preparation and characterization of a decellularized cartilage scaffold for ear cartilage reconstruction, Biomed. Mater. 10 (2015) 015010.
[39] D. Wendt, S.A. Riboldi, M. Cioffi, I. Martin, Bioreactors in Tissue Engineering: Scientific Challenges and Clinical Perspectives, Springer, Berlin Heidelberg, 2008 1–27.
[40] P. Delaere, J. Vranckx, G. Verleden, P. De Leyn, D. Van Raemdonck, Tracheal allotransplantation after withdrawal of immunosuppressive therapy, N. Engl. J. Med. 362 (2010) 138–145.
[41] D.M. Faulk, S.A. Johnson, L. Zhang, S.F. Badylak, Role of the extracellular matrix in whole organ engineering, J. Cell. Physiol. 229 (2014) 984–989.
[42] R.A. Hopper, K. Woodhouse, J.L. Semple, Acellularization of human placenta with preservation of the basement membrane: a potential matrix for tissue engineering, Ann. Plast. Surg. 51 (2003) 598–602.
[43] P.L. Sánchez, M.E. Fernández-Santos, S. Costanza, A.M. Climent, I. Moscoso, M.A. Gonzalez-Nicolas, R. Sanz-Ruiz, H. Rodríguez, S.M. Kren, G. Garrido, J.L. Escalante, J. Bermejo, J. Elizaga, J. Menarguez, R. Yotti, C. Pérez del Villar, M.A. Espinosa, M.S. Guillem, J.T. Willerson, A. Bernad, R. Matesanz, D.A. Taylor, F. Fernández-Avilés,

Acellular human heart matrix: a critical step toward whole heart grafts, Biomaterials 61 (2015) 279–289.
[44] R.C. Hill, E.A. Calle, M. Dzieciatkowska, L.E. Niklason, K.C. Hansen, Quantification of extracellular matrix proteins from a rat lung scaffold to provide a molecular readout for tissue engineering, Mol. Cell. Proteomics 14 (2015) 961–973.
[45] G. Mazza, K. Rombouts, A. Rennie Hall, L. Urbani, T. Vinh Luong, W. Al-Akkad, L. Longato, D. Brown, P. Maghsoudlou, A.P. Dhillon, B. Fuller, B. Davidson, K. Moore, D. Dhar, P. De Coppi, M. Malago, M. Pinzani, Decellularized human liver as a natural 3D-scaffold for liver bioengineering and transplantation, Sci. Rep. 7 (2015) 13079.
[46] M.M. Laronda, A.E. Jakus, K.A. Whelan, J.A. Wertheim, R.N. Shah, T.K. Woodruff, Initiation of puberty in mice following decellularized ovary transplant, Biomaterials 50 (2015) 20–29.
[47] A. Lichtenberg, I. Tudorache, S. Cebotari, M. Suprunov, G. Tudorache, H. Goerler, J.-K. Park, D. Hilfiker-Kleiner, S. Ringes-Lichtenberg, M. Karck, G. Brandes, A. Hilfiker, A. Haverich, Preclinical testing of tissue-engineered heart valves re-endothelialized under simulated physiological conditions, Circulation 114 (2006) I–559-I-565.
[48] F.C. Batista, E.L. Batista, Managing soft tissue fenestrations in bone grafting surgery with an acellular dermal matrix: a case report, Int. J. Oral Maxillofac. Implants 16 (2001) 875–879.
[49] D.J. Wainwright, Use of an acellular allograft dermal matrix (AlloDerm) in the management of full-thickness burns, Burns 21 (1995) 243–248.
[50] N.D. Karras, H.A. Tobin, Lip augmentation using an alloderm graft, J. Oral Maxillofac. Surg. 56 (1998) 722–727.
[51] B. Buinewicz, B. Rosen, Acellular cadaveric dermis (AlloDerm): a new alternative for abdominal hernia repair, Ann. Plast. Surg. 52 (2004) 188–194.
[52] H.C. Ott, J.J. Song, Organ engineering based on decellularized matrix scaffolds, Trends Mol. Med. 17 (2011) 424–432.
[53] V.J. Mase, J.R. Hsu, S.e. Wolf, J.C. Wenke, D.G. Baer, J. Owens, S.F. Badylak, T.J. Walters, Clinical application of an acellular biologic scaffold for surgical repair of a large, traumatic quadriceps femoris muscle defect, Orthopedics 33 (2011) 511.
[54] P. Simon, M.T. Kasimir, G. Seebacher, G. Weigel, R. Ullrich, U. Salzer-Muhar, E. Rieder, E. Wolner, Early failure of the tissue engineered porcine heart valve SYNERGRAFT® in pediatric patients, Eur. J. Cardiothorac. Surg. 23 (2003) 1002–1006.
[55] K. Schenke-Layland, Non-invasive multiphoton imaging of extracellular matrix structures, J. Biophotonics 1 (2008) 451–462.
[56] M. Votteler, D.A. Carvajal Berrio, M. Pudlas, H. Walles, U.A. Stock, K. Schenke-Layland, Raman spectroscopy for the non-contact and non-destructive monitoring of collagen damage within tissues, J. Biophotonics 5 (2012) 47–56.
[57] M. Votteler, D.A. Carvajal Berrio, M. Pudlas, H. Walles, K. Schenke-Layland, Non-contact, label-free monitoring of cells and extracellular matrix using Raman spectroscopy, J. Vis. Exp. (2012) e3977.
[58] M. Pudlas, E. Brauchle, T.J. Klein, D.W. Hutmacher, K. Schenke-Layland, Non-invasive identification of proteoglycans and chondrocyte differentiation state by Raman microspectroscopy, J. Biophotonics 6 (2013) 205–211.
[59] K. Schenke-Layland, U.A. Stock, A. Nsair, J. Xie, E. Angelis, C.G. Fonseca, R. Larbig, A. Mahajan, K. Shivkumar, M.C. Fishbein, W.R. MacLellan, Cardiomyopathy is associated with structural remodelling of heart valve extracellular matrix, Eur. Heart J. 30 (2009) 2254–2265.
[60] P. Macchiarini, P. Jungebluth, T. Go, M.A. Asnaghi, L.E. Rees, T.A. Cogan, A. Dodson, J. Martorell, S. Bellini, P.P. Parnigotto, S.C. Dickinson, A.P. Hollander, S. Mantero, M.T. Conconi, M.A. Birchall, Clinical transplantation of a tissue-engineered airway, Lancet 13 (2008) 2023–2030.
[61] T.D. Johnson, R.C. Hill, M. Dzieciatkowska, V. Nigam, A. Behfar, K.L. Christman, K.C. Hansen, Quantification of decellularized human myocardial matrix: a comparison of six patients, Proteomics Clin. Appl. (2015), http://dx.doi.org/10.1002/prca.201500048.
[62] C.A. Pacak, A.A. MacKay, D.B. Cowan, An improved method for the preparation of type I collagen from skin, J. Vis. Exp. (2014) e51011.
[63] T. Tharmalingam, K. Sunley, M. Spearman, M. Butler, Enhanced production of human recombinant proteins from CHO cells grown to high densities in macroporous microcarriers, Mol. Biotechnol. 49 (2011) 263–276.
[64] G.C. Yeo, B. Aghaei-Ghareh-Bolagh, E.P. Brackenreg, M.A. Hiob, P. Lee, A.S. Weiss, Fabricated elastin, Adv. Healthcare Mater. (2015), http://dx.doi.org/10.1002/adhm.201400781.
[65] M. Nagaoka, H.-L. Jiang, T. Hoshiba, T. Akaike, C.-S. Cho, Application of recombinant fusion proteins for tissue engineering, Ann. Biomed. Eng. 38 (2010) 683–693.
[66] N. Uchida, S. Sivaraman, N.J. Amoroso, W.R. Wagner, A. Nishiguchi, M. Matsusaki, M. Akashi, J. Nagatomi, Nanometer-sized extracellular matrix coating on polymer-based scaffold for tissue engineering applications, J. Biomed. Mater. Res. A (2015), http://dx.doi.org/10.1002/jbm.a.35544.
[67] J. Ma, N. Zhao, D. Zhu, Sirolimus-eluting dextran and polyglutamic acid hybrid coatings on AZ31 for stent applications, J. Biomater. Appl. (2015), http://dx.doi.org/10.1177/0885328215596324.
[68] K. Schenke-Layland, K.E. Rhodes, E. Angelis, Y. Butylkova, S. Heydarkhan-Hagvall, C. Gekas, R. Zhang, J.I. Goldhaber, H.K. Mikkola, K. Plath, W.R. MacLellan, Reprogrammed mouse fibroblasts differentiate into cells of the cardiovascular and hematopoietic lineages, Stem Cells 26 (2008) 1537–1546.
[69] C. Rentsch, B. Rentsch, S. Heinemann, R. Bernhardt, B. Bischoff, Y. Foerster, D. Scharnweber, S. Rammelt, ECM inspired coating of embroidered 3D scaffolds enhances calvaria bone regeneration, BioMed Res. Int. 2014 (2014) 1–15.
[70] J.L. Steiner, C.H. Lang, Dysregulation of skeletal muscle protein metabolism by alcohol, Am. J. Physiol. Endocrinol. Metab. 308 (2015) E699–E712.
[71] M.H. Kollef, B. Afessa, A. Anzueto, Silver-coated endotracheal tubes and incidence of ventilator-associated pneumonia: the nascent randomized trial, JAMA 300 (2008) 805–813.
[72] A.S. Badami, M.R. Kreke, M.S. Thompson, J.S. Riffle, A.S. Goldstein, Effect of fiber diameter on spreading, proliferation, and differentiation of osteoblastic cells on electrospun poly(lactic acid) substrates, Biomaterials 27 (2006) 596–606.
[73] S. Hinderer, E. Brauchle, K. Schenke-Layland, Generation and assessment of functional biomaterial scaffolds for applications in cardiovascular tissue engineering and regenerative medicine, Adv. Healthcare Mater. (2015), http://dx.doi.org/10.1002/adhm.201400762.
[74] T.J. Sill, H.A. von Recum, Electrospinning: applications in drug delivery and tissue engineering, Biomaterials 29 (2008) 1989–2006.
[75] S. Agarwal, J.H. Wendorff, A. Greiner, Progress in the field of electrospinning for tissue engineering applications, Adv. Mater. 21 (2009) 3343–3351.
[76] S. Hinderer, M. Schesny, A. Bayrak, B. Ibold, M. Hampel, T. Walles, U.A. Stock, M. Seifert, K. Schenke-Layland, Engineering of fibrillar decorin matrices for a tissue-engineered trachea, Biomaterials 33 (2012) 5259–5266.
[77] E.M. Jeffries, R.A. Allen, J. Gao, M. Pesce, Y. Wang, Highly elastic and suturable electrospun poly(glycerol sebacate) fibrous scaffolds, Acta Biomater. (2015), http://dx.doi.org/10.1016/j.actbio.2015.02.005.
[78] S.G. Kumbar, R. James, S.P. Nukavarapu, C.T. Laurencin, Electrospun nanofiber scaffolds: engineering soft tissues, Biomed. Mater. 3 (2008) 034002.
[79] R. Rai, M. Tallawi, C. Frati, A. Falco, A. Gervasi, F. Quaini, J.A. Roether, T. Hochburger, D.W. Schubert, L. Seik, N. Barbani, L. Lazzeri, E. Rosellini, A.R. Boccaccini, Bioactive electrospun fibers of poly(glycerol sebacate) and poly(ε-caprolactone) for cardiac patch application, Adv. Healthcare Mater. (2015), http://dx.doi.org/10.1002/adhm.201500154.
[80] L. Huang, R.P. Apkarian, E.L. Chaikof, High-resolution analysis of engineered type I collagen nanofibers by electron microscopy, Scanning 23 (2001) 372–375.
[81] X. Wen, Y. Wang, Z. Guo, H. Meng, J. Huang, L. Zhang, B. Zhao, Q. Zhao, Y. Zheng, J. Peng, Cauda equina-derived extracellular matrix for fabrication of nanostructured hybrid scaffolds applied to neural tissue engineering, Tissue Eng. Part A 21 (2014) 1095–1105.
[82] J. Liu, L. Argenta, M. Morykwas, W.D. Wagner, Properties of single electrospun poly(diol citrate)-collagen-proteoglycan nanofibers for arterial repair and in applications requiring viscoelasticity, J. Biomater. Appl. 28 (2014) 729–738.
[83] S.S. Rao, M.T. Nelson, R. Xue, J.K. DeJesus, M.S. Viapiano, J.J. Lannutti, A. Sarkar, J.O. Winter, Mimicking white matter tract topography using core-shell electrospun nanofibers to examine migration of malignant brain tumors, Biomaterials 34 (2013) 5181–5190.
[84] R. Huang, W. Li, X. Lv, Z. Lei, Y. Bian, H. Deng, H. Wang, J. Li, X. Li, Biomimetic LBL structured nanofibrous matrices assembled by chitosan/collagen for promoting wound healing, Biomaterials 53 (2015) 58–78.
[85] E. Hoch, G.E.M. Tovar, K. Borchers, Bioprinting of artificial blood vessels: current approaches towards a demanding goal, Eur. J. Cardiothorac. Surg. 46 (2014) 767–778.
[86] S.V. Murphy, A. Atala, 3D bioprinting of tissues and organs, Nat. Biotechnol. 32 (2014) 773–785.
[87] C.C. Chang, L. Krishnan, S.S. Nunes, K.H. Church, L.T. Edgar, E.D. Boland, J.A. Weiss, S.K. Williams, J.B. Hoying, Determinants of microvascular network topologies in implanted neovasculatures, Arterioscler. Thromb. Vasc. Biol. 32 (2012) 5–14.
[88] X. Cui, T. Boland, Human microvasculature fabrication using thermal inkjet printing technology, Biomaterials 30 (2009) 6221–6227.
[89] E. Hoch, T. Hirth, G.E.M. Tovar, K. Borchers, Chemical tailoring of gelatin to adjust its chemical and physical properties for functional bioprinting, J. Mater. Chem. B 1 (2013) 5675–5685.
[90] Y. Sun, Q. Jallerat, J.M. Szymanski, A.W. Feinberg, Conformal nanopatterning of extracellular matrix proteins onto topographically complex surfaces, Nat. Methods 12 (2015) 134–136.
[91] S. Joo, J.Y. Kim, E. Lee, N. Hong, W. Sun, Y. Nam, Effects of ECM protein micropatterns on the migration and differentiation of adult neural stem cells, Sci. Rep. 5 (2015) 13043.
[92] S.G. Ricoult, A.S. Nezhad, M. Knapp-Mohammady, T.E. Kennedy, D. Juncker, Humidified microcontact printing of proteins: universal patterning of proteins on both low and high energy surfaces, Langmuir 30 (2014) 12002–12010.
[93] D.A. Zopf, S.J. Hollister, M.E. Nelson, R.G. Ohye, G.E. Green, Bioresorbable airway splint created with a three-dimensional printer, N. Engl. J. Med. 368 (2013) 2043–2045.
[94] C.M. O'Brien, B. Holmes, S. Faucett, L.G. Zhang, Three-dimensional printing of nanomaterial scaffolds for complex tissue regeneration, Tissue Eng. Part B Rev. 21 (2014) 103–114.
[95] A. Skardal, D. Mack, E. Kapetanovic, A. Atala, J.D. Jackson, J. Yoo, S. Soker, Bioprinted amniotic fluid-derived stem cells accelerate healing of large skin wounds, Stem Cells Transl. Med. 1 (2012) 792–802.
[96] A. Waterhouse, S.G. Wise, M.K. Ng, A.S. Weiss, Elastin as a nonthrombogenic biomaterial, Tissue Eng. Part. B Rev. 17 (2011) 93–99.
[97] J. Yu, K.T. Du, Q. Fang, Y. Gu, S.S. Mihardja, R.E. Sievers, J.C. Wu, R.J. Lee, The use of human mesenchymal stem cells encapsulated in RGD modified alginate microspheres in the repair of myocardial infarction in the rat, Biomaterials 31 (2010) 7012–7020.
[98] M.M.C. Bastings, S. Koudstaal, R.E. Kieltyka, Y. Nakano, A.C.H. Pape, D.A.M. Feyen, F.J. van Slochteren, P.A. Doevendans, J.P.G. Sluijter, E.W. Meijer, S.A.J. Chamuleau, P.Y.W. Dankers, A fast pH-switchable and self-healing supramolecular hydrogel carrier for guided, local catheter injection in the infarcted myocardium, Adv. Healthcare Mater. 3 (2014) 70–78.
[99] M. Habib, K. Shapira-Schweitzer, O. Caspi, A. Gepstein, G. Arbel, D. Aronson, D. Seliktar, L. Gepstein, A combined cell therapy and in-situ tissue-engineering approach for myocardial repair, Biomaterials 32 (2011) 7514–7523.
[100] K. Xu, K. Narayanan, F. Lee, K.H. Bae, S. Gao, M. Kurisawa, Enzyme-mediated hyaluronic acid–tyramine hydrogels for the propagation of human embryonic

stem cells in 3D, Acta Biomater. (2015), http://dx.doi.org/10.1016/j.actbio.2015.06.026.
[101] E.E. Antoine, P.P. Vlachos, M.N. Rylander, Tunable collagen I hydrogels for engineered physiological tissue micro-environments, PLoS ONE 10 (2015) e0122500.
[102] S. Michal, R. Zax, A. Alona, S. Fleischer, A. Shapira, T. Dvir, Omentum ECM-based hydrogel as a platform for cardiac cell delivery, Biomed. Mater. 10 (2015) 034106.
[103] R.M. Wang, K.L. Christman, Decellularized myocardial matrix hydrogels: in basic research and preclinical studies, Adv. Drug Deliv. Rev. (2015), http://dx.doi.org/10.1016/j.addr.2015.06.002.
[104] TETEC, Novocart Inject, http://www.tetec-ag.de1.11.2015.
[105] K. Schenke-Layland, F. Rofail, S. Heydarkhan, J.M. Gluck, N.P. Ingle, E. Angelis, C.-H. Choi, W.R. MacLellan, R.E. Beygui, R.J. Shemin, S. Heydarkhan-Hagvall, The use of three-dimensional nanostructures to instruct cells to produce extracellular matrix for regenerative medicine strategies, Biomaterials 30 (2009) 4665–4675.
[106] K. Matsuura, R. Utoh, K. Nagase, T. Okano, Cell sheet approach for tissue engineering and regenerative medicine, J. Control. Release 190 (2014) 228–239.
[107] N. L'Heureux, N. Dusserre, G. Konig, B. Victor, P. Keire, T.N. Wight, N.A.F. Chronos, A.E. Kyles, C.R. Gregory, G. Hoyt, R.C. Robbins, T.N. McAllister, Human tissue-engineered blood vessels for adult arterial revascularization, Nat. Med. 12 (2006) 361–365.
[108] K. Nishida, M. Yamato, Y. Hayashida, K. Watanabe, K. Yamamoto, E. Adachi, S. Nagai, A. Kikuchi, N. Maeda, H. Watanabe, T. Okano, Y. Tano, Corneal reconstruction with tissue-engineered cell sheets composed of autologous oral mucosal epithelium, N. Engl. J. Med. 351 (2004) 1187–1196.
[109] Y. Sawa, S. Miyagawa, T. Sakaguchi, T. Fujita, A. Matsuyama, A. Saito, T. Shimizu, T. Okano, Tissue engineered myoblast sheets improved cardiac function sufficiently to discontinue LVAS in a patient with DCM: report of a case, Surg. Today 42 (2012) 181–184.
[110] M. Sato, M. Yamato, K. Hamahashi, T. Okano, J. Mochida, Articular cartilage regeneration using cell sheet technology, Anat. Rec. 297 (2014) 36–43.
[111] N. L'Heureux, T.N. McAllister, L.M. de la Fuente, Tissue-engineered blood vessel for adult arterial revascularization, N. Engl. J. Med. 357 (2007) 1451–1453.
[112] K. Sakaguchi, T. Shimizu, T. Okano, Construction of three-dimensional vascularized cardiac tissue with cell sheet engineering, J. Control. Release 205 (2015) 83–88.
[113] EU-AMCARE, www.amcare.eu04.08.2015.
[114] S.-N. Park, J.K. Kim, H. Suh, Evaluation of antibiotic-loaded collagen-hyaluronic acid matrix as a skin substitute, Biomaterials 25 (2004) 3689–3698.
[115] Y. Yu, M.J. Brouillette, D. Seol, H. Zheng, J.A. Buckwalter, J.A. Martin, Use of recombinant human stromal cell-derived factor 1α-loaded fibrin/hyaluronic acid hydrogel networks to achieve functional repair of full-thickness bovine articular cartilage via homing of chondrogenic progenitor cells, Arthritis Rheumatol. 67 (2015) 1274–1285.
[116] E. Byun, H. Lee, Enhanced loading efficiency and sustained release of doxorubicin from hyaluronic acid/graphene oxide composite hydrogels by a mussel-inspired catecholamine, J. Nanosci. Nanotechnol. 14 (2014) 7395–7401.
[117] R. Heo, J.-S. Park, H.J. Jang, S.-H. Kim, J.M. Shin, Y.D. Suh, J.H. Jeong, D.-G. Jo, J.H. Park, Hyaluronan nanoparticles bearing γ-secretase inhibitor: in vivo therapeutic effects on rheumatoid arthritis, J. Control. Release 192 (2014) 295–300.
[118] S.R. MacEwan, A. Chilkoti, Elastin-like polypeptides: biomedical applications of tunable biopolymers, Pept. Sci. 94 (2010) 60–77.
[119] M.R. Dreher, D. Raucher, N. Balu, O. Michael Colvin, S.M. Ludeman, A. Chilkoti, Evaluation of an elastin-like polypeptide-doxorubicin conjugate for cancer therapy, J. Control. Release 91 (2003) 31–43.
[120] R.A. Perez, M. Kim, T.-H. Kim, J.-H. Kim, J.H. Lee, J.-H. Park, J.C. Knowles, H.-W. Kim, Utilizing core-shell fibrous collagen-alginate hydrogel cell delivery system for bone tissue engineering, Tissue Eng. Part A 20 (2013) 103–114.
[121] M. Peroglio, S. Grad, D. Mortisen, C. Sprecher, S. Illien-Jünger, M. Alini, D. Eglin, Injectable thermoreversible hyaluronan-based hydrogels for nucleus pulposus cell encapsulation, Eur. Spine J. 21 (2012) 839–849.
[122] A.C. Gaffey, M.H. Chen, C.M. Venkataraman, A. Trubelja, C.B. Rodell, P.V. Dinh, G. Hung, J.W. MacArthur, R.V. Soopan, J.A. Burdick, P. Atluri, Injectable shear-thinning hydrogels used to deliver endothelial progenitor cells, enhance cell engraftment, and improve ischemic myocardium, J. Thorac. Cardiovasc. Surg. (2015), http://dx.doi.org/10.1016/j.jtcvs.2015.07.035.
[123] T. Niethammer, M. Pietschmann, A. Horng, B. Roßbach, A. Ficklscherer, V. Jansson, P. Müller, Graft hypertrophy of matrix-based autologous chondrocyte implantation: a two-year follow-up study of NOVOCART 3D implantation in the knee, Knee Surg. Sports Traumatol. Arthrosc. 22 (2014) 1329–1336.
[124] N.-Y. Choi, B.-W. Kim, W.-J. Yeo, H.-B. Kim, D.-S. Suh, J.-S. Kim, Y.-S. Kim, Y.-H. Seo, J.-Y. Cho, C.-W. Chun, H.-S. Park, A. Shetty, S.-J. Kim, Gel-type autologous chondrocyte (Chondron™) implantation for treatment of articular cartilage defects of the knee, BMC Musculoskelet. Disord. 11 (2010) 1–8.
[125] L. Mazzone, L. Pontiggia, E. Reichmann, N. Ochsenbein-Kölble, U. Moehrlen, M. Meuli, Experimental tissue engineering of fetal skin, Pediatr. Surg. Int. 30 (2014) 1241–1247.
[126] S.H. Ranganath, C.-H. Wang, Biodegradable microfiber implants delivering paclitaxel for post-surgical chemotherapy against malignant glioma, Biomaterials 29 (2008) 2996–3003.
[127] M.A. Ali, K. Mondal, C. Singh, B. Dhar Malhotra, A. Sharma, Anti-epidermal growth factor receptor conjugated mesoporous zinc oxide nanofibers for breast cancer diagnostics, Nanoscale 7 (2015) 7234–7245.
[128] Z. Wang, Y. Qian, L. Li, L. Pan, L.W. Njunge, L. Dong, L. Yang, Evaluation of emulsion electrospun polycaprolactone/hyaluronan/epidermal growth factor nanofibrous scaffolds for wound healing, J. Biomater. Appl. (2015), http://dx.doi.org/10.1177/0885328215586907.
[129] M. Sampath, R. Lakra, P. Korrapati, B. Sengottuvelan, Curcumin loaded poly(lactic-co-glycolic) acid nanofiber for the treatment of carcinoma, Colloids Surf. B: Biointerfaces 117 (2014) 128–134.
[130] B. Ardeshirzadeh, N.A. Anaraki, M. Irani, L.R. Rad, S. Shamshiri, Controlled release of doxorubicin from electrospun PEO/chitosan/graphene oxide nanocomposite nanofibrous scaffolds, Mater. Sci. Eng. C Mater. Biol. Appl. 48 (2015) 384–390.
[131] E. Yan, Y. Fan, Z. Sun, J. Gao, X. Hao, S. Pei, C. Wang, L. Sun, D. Zhang, Biocompatible core-shell electrospun nanofibers as potential application for chemotherapy against ovary cancer, Mater. Sci. Eng. C Mater. Biol. Appl. 41 (2014) 217–223.
[132] Y. Wang, Z. Li, P. Shao, S. Hao, W. Wang, Q. Yang, B. Wang, A novel multiple drug release system in vitro based on adjusting swelling core of emulsion electrospun nanofibers with core-sheath structure, Mater. Sci. Eng. C Mater. Biol. Appl. 44 (2014) 109–116.
[133] G. Yang, J. Wang, Y. Wang, L. Li, X. Guo, S. Zhou, An implantable active-targeting micelle-in-nanofiber device for efficient and safe cancer therapy, ACS Nano 9 (2015) 1161–1174.
[134] T.G. Kim, H. Shin, D.W. Lim, Biomimetic scaffolds for tissue engineering, Adv. Funct. Mater. 22 (2012) 2446–2468.
[135] K. Kyburz, K. Anseth, Synthetic mimics of the extracellular matrix: how simple is complex enough? Ann. Biomed. Eng. 43 (2015) 489–500.
[136] M. Frydrych, S. Román, S. MacNeil, B. Chen, Biomimetic poly(glycerol sebacate)/poly(L-lactic acid) blend scaffolds for adipose tissue engineering, Acta Biomater. 18 (2015) 40–49.
[137] R.A. Neal, S.G. McClugage, M.C. Link, L.S. Sefcik, R.C. Ogle, E.A. Botchwey, Laminin nanofiber meshes that mimic morphological properties and bioactivity of basement membranes, Tissue Eng. Part C Methods 15 (2008) 11–21.
[138] E. Migliorini, D. Thakar, R. Sadir, T. Pleiner, F. Baleux, H. Lortat-Jacob, L. Coche-Guerente, R. Richter, Well-defined biomimetic surfaces to characterize glycosaminoglycan-mediated interactions on the molecular, supramolecular and cellular levels, Biomaterials 35 (2014) 8903–8915.
[139] S.G. Wise, M.J. Byrom, A. Waterhouse, P.G. Bannon, M.K.C. Ng, A.S. Weiss, A multilayered synthetic human elastin/polycaprolactone hybrid vascular graft with tailored mechanical properties, Acta Biomater. 7 (2011) 295–303.
[140] Y. Xu, J. Wu, H. Wang, H. Li, N. Di, L. Song, S. Li, D. Li, Y. Xiang, W. Liu, X. Mo, Q. Zhou, Fabrication of electrospun poly(L-lactide-co-ε-caprolactone)/collagen nanoyarn network as a novel, three-dimensional, macroporous, aligned scaffold for tendon tissue engineering, Tissue Eng. Part C Methods 19 (2013) 925–936.
[141] Y. Shin, J. Lee, L. Jin, M. Kim, Y.-J. Kim, J. Hyun, T.-G. Jung, S. Hong, D.-W. Han, Stimulated myoblast differentiation on graphene oxide-impregnated PLGA-collagen hybrid fibre matrices, J. Nanobiotechnol. 13 (2015) 21.
[142] R. Fischer, M. McCoy, S. Grant, Electrospinning collagen and hyaluronic acid nanofiber meshes, J. Mater. Sci. Mater. Med. 23 (2012) 1645–1654.
[143] N.W. Garrigues, D. Little, J. Sanchez-Adams, D.S. Ruch, F. Guilak, Electrospun cartilage-derived matrix scaffolds for cartilage tissue engineering, J Biomed Mater Res A 102 (2014) 3998–4008.
[144] M.P. Francis, P.C. Sachs, P.A. Madurantakam, S.A. Sell, L.W. Elmore, G.L. Bowlin, S.E. Holt, Electrospinning adipose tissue-derived extracellular matrix for adipose stem cell culture, J. Biomed. Mater. Res. A 100A (2012) 1716–1724.
[145] S. Zhong, W.E. Teo, X. Zhu, R. Beuerman, S. Ramakrishna, L.Y. Yung, Formation of collagen-glycosaminoglycan blended nanofibrous scaffolds and their biological properties, Biomacromolecules 6 (2005) 2998–3004.